Remarks/Arguments:

Claims 4, 9, 11, 14-16, 20, 22-25, 29, 31-34, 38, 40-43, 48, 50-51, 54-57, 62, 64-73, and 75-80 are canceled without prejudice. Claims 1, 17, 26, 35, 44, 58, 74, 84, 86, 88, 93, and 96 are amended. Support for these amendments can be found throughout the application as originally filed and are discussed in detail below. No new matter is introduced.

Claims 1-3, 5-8, 10, 12-13, 17-19, 21, 26-28, 30, 35-37, 39, 44-47, 49, 52-53, 58-61, 63, 74, and 81-96 are pending. Reexamination and reconsideration of the application, as amended, are respectfully requested.

CLAIM REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH - ENABLEMENT

Claims 1-8, 10-19, 21-28, 30-37, 39-47, 49-61, 63-70, 74-80, and 93-96 stand rejected for lack of enablement. Applicants respectfully point out that claim 4 was previously withdrawn from consideration and claims 11, 14-16, 22-25, 31-34, 40-43, 50-51, 54-57, 64-70, and 75-80 previously canceled. These claims will not be discussed below.

(1) The Examiner rejected claim 1 primarily for reciting "one or more DNA markers in the *12q22-23* region extending from D12S1657 to D12S346." See page 3, lines 1-8 of the Office Action. Without acquiescence in the Examiner's rejection, Applicants have amended claim 1 to recite "one or more DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346."

Claim 1, as amended, is directed to a method of detecting DNA markers in the *12q22-23* region. The method comprises: providing a sample containing DNA from a human subject, wherein the DNA exists as acellular DNA in the subject; and detecting one or more DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346 on the DNA. This claim is fully enabled by the specification. For example, Example 2 in the specification describes

collecting blood from human subjects, separating serum from cells, and extracting DNA from the serum, and detecting D12S1657, D12S393, D12S1706, and D12S346 markers on the DNA (page 31, line 9 – page 37, line 13).

(2) The Examiner rejected claim 6 apparently because he assumed that responders are melanoma free (page 11, lines 1-2 of the Office Action). The Examiner asserted that, since there is no significant difference of LOH of DNA markers in post-BC serum between responders (whom the Examiner believed to be melanoma free) and non-responders (i.e., who remained to have melanoma) (page 36, lines 12-14 of the specification), the DNA markers (D12S1657, D12S393, D12S1706, and D12S346) are not associated with melanoma after chemotherapy. See page 6, lines 3-6 and page 7, lines 10-12 of the Office Action. Applicants respectfully disagree.

Contrary to the Examiner's assumption, responders are not necessarily melanoma free. As shown in Table 4 of the specification (page 31, line 19 – page 32, line 9), the responder group includes patients who showed complete response (CR), partial response (PR), and stable disease (SD). The specification further states:

> Patients were divided into two groups (responders and non-responders) based on response criteria developed by the Response Evaluation Criteria in Solid Tumors Group (Therasse et al., 2000, J. Natl. Cancer Inst. 92:205-216).

A copy of Therasse et al., 2000, J. Natl. Cancer Inst. 92:205-216 is attached hereto as Exhibit A. According to this article, when evaluating target lesions, "complete response" refers to the disappearance of all target lesions, "partial response" refers to at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter, and "stable disease" refers to neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started (page 208, right column, section 3.2.1., lines 6-16). Clearly, responders in the "partial response" and "stable disease" subgroups

would not be melanoma free. Moreover, the article points out that some tumor lesions are not measurable by imaging techniques such as CT scans (page 207, right column, section 2.1., lines 2-9). Thus, disappearance of target lesions in a patient in the "complete response" subgroup does not necessarily mean that the patient has become melanoma free; rather, target lesions may disappear simply because they have become non-measurable.

Taken together, the Examiner's assumption that responders are melanoma free is erroneous. So is his conclusion drawn from the assumption that the DNA markers (D12S1657, D12S393, D12S1706, and D12S346) are not associated with melanoma after chemotherapy.

(3) The Examiner rejected claims 17 and 26 because the specification teaches that there was no significant difference in LOH of DNA markers associated with stage III versus stage IV melanoma patients or ITM versus RLM stage III melanoma patients (page 12, lines 12-21 of the Office Action). Applicants respectfully traverse.

Claim 17 is drawn to a method of staging melanoma or colon cancer where LOH of DNA markers indicates that the probability for a subject to suffer from a metastatic cancer is higher than the probability for the subject to suffer from a primary cancer. Claim 26 is drawn to a method of monitoring progression of melanoma or colon cancer where LOH of DNA markers indicates that the probability for a subject to suffer from a progressing cancer is higher than the probability for the subject to suffer from a non-progressing cancer. The specification teaches that LOH of DNA markers was significantly higher in metastatic melanoma or colon cancer than in primary melanomas or colon cancer (page 24, lines 11-12 and page 37, Table 7), thereby enabling claims 17 and 26. In this connection, Applicants point out that claims 17 and 26 do not recite distinctions between stage III and stage IV or ITM and RLM cancers. Therefore, that no significant difference

was found in LOH of DNA markers between stage III and stage IV or ITM and RLM cancers is irrelevant.

(4) The Examiner rejected claims 35 and 58 because the specification teaches that there is not a statistically significant relationship between LOH of DNA markers and therapeutic response after chemotherapy (page 7, lines 5-8 of the Office Action). Applicants respectfully disagree. More specifically, claims 35 and 58 involve determination of the efficacy of a biochemotherapy and the probability of responsiveness to a biochemotherapy based on LOH of DNA markers in a sample from a melanoma patient prior to administration of the biochemotherapy. As such, that no statistically significant relationship was found between LOH of DNA markers and therapeutic response after chemotherapy is irrelevant.

Further, the Examiner stated that the specification teaches LOH of any of the DNA markers recited in claims 35 and 58, while the election was drawn to LOH of all of the markers (page 13, lines 17-19 of the Office Action). Applicants respectfully point out that the election was drawn to analysis of all of the recited DNA markers (D12S1657, D12S393, D12S1706, and D12S346). Consistent with the election, the specification teaches analysis of all four markers, while LOH of any of the markers is associated with the efficacy of a biochemotherapy and the probability of responsiveness to a biochemotherapy (Figure 7).

(5) The Examiner rejected claim 44 because he believed that, while stage III melanoma with RLM was statistically correlated with APAF-1 status, metastatic melanoma with ITM was not (page 5, lines 16-21 of the Office Action). The Examiner also stated that the specification is silent on stage IV in this regard (page 5, line 21 – page 6, line 2 of the Office Action). Applicants respectfully point out that the Examiner's understanding of the specification is erroneous. More specifically, contrary to the Examiner's assertions, the specification teaches that, in patients with stage III/IV melanoma, LOH of DNA markers was significantly associated with a decreased overall survival (page 26, lines 12-15). The

specification further teaches that LOH of DNA markers in RLM had a significantly worse survival outcome compared to LOH of DNA markers in ITM (page 27, lines 1-3). However, this does not mean that LOH of DNA markers in ITM was not associated with a decreased overall survival, even though the association was not as strong as in RLM.

The Examiner also rejected claim 44 for reciting "any" sample (page 13, line 22 - page 14, line 4 of the Office Action). In addition, the Examiner stated that it is unclear how a patient that has responded to treatment would be considered to have a low probability of survival (page 14, lines 5-9 of the Office Action). Without acquiescence in the Examiner's rejection, Applicants have amended claim 44 to recite "a melanoma tissue sample or a body fluid sample" and "wherein LOH of any of D12S1657, D12S393, D12S1706, and D12S346 indicates that the subject has a low probability of survival if the subject has not responded to a biochemotherapy." This amendment is supported by the specification, e.g., at page 26, lines 6-15 and page 36, lines 16-18.

(6) The Examiner rejected claim 93 primarily because the specification does not teach that LOH of DNA markers are statistically correlated with colon or breast cancer. Applicants respectfully disagree. As presented in Applicants' response to the Office Action dated October 31, 2006, Example 2 at page 31, line 9 – page 37, line 12 of the specification demonstrates that, compared to the control DNA obtained from the patients' peripheral blood lymphocytes, LOH of DNA markers was found in serum samples from colon and breast cancer patients. Note that, contrary to the Examiner's assertion that the specification does not teach use of peripheral blood lymphocytes as a control (page 6, lines 1-3 of the Office Action), the specification states at page 32, lines 27-29 "[c]ontrol DNA for each melanoma patient[s] was obtained from the respective peripheral blood lymphocytes." Since LOH of DNA markers was 0% on the control DNA (Figure 6), LOH of DNA markers

was significantly higher in colon and breast cancer samples because the p value would be less than 0.05.

With regard to the Examiner's comment that the *12q22-23* region is much larger than APAF-1 (page 11, lines 12-14 of the Office Action), Applicants respectfully submit that the APAF-1 status was determined by analysis of DNA markers D12S1657, D12S393, D12S1706, and D12S346 encompassing the *12q22-23* region (page 33, lines 1-4 of the specification).

With regard to the Examiner's comment that 28 patients is not a large enough sample to suggest the significance of Applicants' finding on breast cancer (page 11, lines 16-18 of the Office Action), Applicants respectfully submit that the Examiner failed to provide any support to his assertion.

With regard to the Examiner's comment that Tables 6 and 7 appear to relate to biopsies of colon and breast caners (page 11, lines 18-20 of the Office Action), Applicants respectfully submit that Example 2 in the specification describes LOH of DNA markers on acellular DNA (page 32, lines 22-29).

(7) The Examiner also rejected the claims for reciting "any" subject (page 4, lines 3-5 of the Office Action). Applicants respectfully submit that all claims are drawn to "human subject," not "any" subject.

The Examiner further rejected the claims for reciting "brain" cancer (page 3, lines 8-9). Without acquiescence in the Examiner's rejection, Applicants have deleted "brain cancer" from claim 86.

With regard to the Examiner's conclusion that chemotherapy results in LOH of DNA markers (page 6, lines 6-7 of the Office Action), Applicants respectfully submit that this conclusion is inconsistent with the data for the non-respondent group (Figure 7).

With regard to the Examiner's comment that the specification does not teach that LOH of DNA markers results in melanoma or any other cancer (page 10, lines 17-21 of the Office Action), Applicants respectfully submit that whether LOH of

DNA markers results in melanoma or any other cancer is irrelevant, as long as it can serve as a marker for melanoma, colon, and breast cancer as taught by the specification.

In view of the forgoing, Applicants submit that claims 1, 6, 17, 26, 35, 44, 58, and 93, as well as their dependent claims, are fully enabled by the specification. Withdrawal of the rejections is respectfully requested.

CLAIM REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH – WRITTEN DESCRIPTION

Claims 1-5 stand rejected for lack of written description because claim 1 recites "any" markers in the *12q22-23* region extending from D12S1657 to D12S346. Applicants respectfully point out that claim 4 was previously withdrawn from consideration and will not be discussed below.

Without acquiescence in the Examiner's rejections, Applicants have amended claim 1 to recite "DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346." This amendment is supported by the specification, e.g., at page 3, lines 12-14. Applicants submit that the rejections have been overcome by the amendment. Withdrawal of the rejection is respectfully requested.

CLAIM REJECTIONS UNDER 35 USC § 112, SECOND PARAGRAPH

Claims 6-10, 12-13, 17-19, 21, 26-28, 30, 35-37, 29 (Applicants believe that the Examiner meant 39), 44-47, 49, 52-53, 58-61, 63, 74-80, and 82-96 stand rejected as being indefinite. Applicants respectfully point out that claim 9 was previously withdrawn from consideration and claims 75-80 previously canceled. Claims 9 and 75-80 will not be discussed below.

More specifically, the Examiner asserted that claim 74 recites "any" combination of the markers. Without acquiescence in the Examiner's rejection, Applicants have amended claim 74 to recite "the" combination of the markers.

Further, the Examiner rejected claims 6, 17, 26, 35, 44, 58, and 93 for reciting "including" and suggested replacing "including" with either "comprising" or "consisting [of]". Applicants respectfully traverse. As shown in Exhibit B, a printout of the definition of the word "include" in Merriam-Webster Online Dictionary, "include" means "comprise as a part of a whole or group" (definition 2). As such, the meaning of the word "including" is not ambiguous at all to one skilled in the art, and no amendment is necessary.

In view of the forgoing, Applicants submit that claims 1, 6, 17, 26, 35, 44, 58, and 93, their dependent claims 7-8, 10, 12-13, 18-19, 21, 27-28, 30, 36-37, 39, 45-47, 49, 52-53, 59-61, 63, and 82-96, and claim 74 particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Withdrawal of the rejections is respectfully requested.

CLAIM REJECTIONS UNDER 35 USC § 102

Claims 17, 21-22, 26, 30, 35, 39, 58-59, 63-64, and 74 stand rejected as being anticipated by Soengas et al. (2001) Nature 409:207-211 ("Soengas"). Applicants respectfully point out that claims 22 and 64 were previously canceled and will not be discussed below.

(1) Without acquiescence in the Examiner's rejections, Applicants have amended claims 17 and 26 to recite "wherein LOH of any of D12S1657, D12S393, D12S1706, and D12S346 indicates that the probability for the subject to suffer from a metastatic cancer is higher than the probability for the subject to suffer from a primary cancer" and "wherein LOH of any of D12S1657, D12S393, D12S1706, and D12S346 indicates that the probability for the subject to suffer from a progressing cancer is higher than the probability for the subject to suffer from a non-progressing

cancer," respectively. This amendment is supported by the specification, e.g., at page 24, lines 11-12. Claims 17 and 26, as amended, are not anticipated by Soengas.

More specifically, as presented in Applicants' response to the Office Action dated October 31, 2006, Soengas provides no information about LOH of APAF-1 in primary melanoma samples. Rather, Soengas only compares the expression of APAF-1 in metastatic melanoma samples and primary melanoma samples (page 207, right column, line 20 – page 208, left column, line 2). However, LOH of APAF-1 does not necessarily correlate with the expression of APAF-1 (Figure 3 of the specification). Therefore, Soengas cannot anticipate claim 17 or 26, because it does not teach that "LOH of any of D12S1657, D12S393, D12S1706, and D12S346 indicates that the probability for the subject to suffer from a metastatic cancer is higher than the probability for the subject to suffer from a primary cancer" or "LOH of any of D12S1657, D12S393, D12S1706, and D12S346 indicates that the probability for the subject to suffer from a progressing cancer is higher than the probability for the subject to suffer from a non-progressing cancer."

(2) Further, without acquiescence in the Examiner's rejections, Applicants have amended claims 35 and 58 to recite "wherein LOH of any of D12S1657, D12S393, D12S1706, and D12S346 indicates poor efficacy of the biochemotherapy in the subject" and "wherein LOH of any of D12S1657, D12S393, D12S1706, and D12S346 indicates a low probability of responsiveness to the biochemotherapy in the subject," respectively. This amendment is supported by Example 2 at page 31, line 9 – page 37, line 12 of the specification. Claims 35 and 58, as amended, are not anticipated by Soengas, because Soengas only finds that APAF-1 negative melanoma cell lines are resistant to ADR, a chemotherapeutic agent (page 209, left column, lines 8-10).

(3) Claim 74 depends from claim 1 and involves detecting DNA markers on DNA existing as acellular DNA in a human subject. As presented in Applicants'

response to the Office Action dated October 31, 2006, Soengas teaches nothing about detecting DNA markers on DNA existing as acellular DNA in a human subject, and therefore cannot anticipate claim 74.

In view of the foregoing, Applicants respectfully submit that claims 17, 26, 35, and 58, as well as their dependent claims and claim 74, are novel over Soengas. The rejection should be withdrawn.

CLAIM REJECTIONS UNDER 35 USC § 103

Claims 1-3, 5-8, 10-13, 17-19, 21-22, 26-28, 30-31, 35-37, 39-40, 58-61, 63-64, 74-78, and 80-96 stand rejected as being unpatentable over Soengas in view of U.S. Patent No. 6,156,504 to Gocke et al. ("Gocke"). Applicants respectfully point out that claims 11, 22, 31, 40, 64, 75-78, and 80 were previously canceled and will not be discussed below.

(1) Claims 1 and 6 involve analyzing and detecting one or more DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346 on DNA existing as acellular DNA in a human subject. Soengas does not teach analyzing and detecting DNA markers on DNA existing as acellular DNA in a human subject. Gocke discloses detection of extracellular tumor-associated nucleic acid in blood plasma or serum in general (genus); however it does not suggest at all that D12S1657, D12S393, D12S1706, and D12S346 (species) are detectable on such DNA. As presented in Applicants' response to the Office Action dated October 31, 2006, because of the unpredictable nature of acellular DNA in a human body, one skilled in the art would not have reasonably expected success in combining Soengas with Gocke to come up with the instant invention. In this connection, Applicants point out that the fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994).

(2) As discussed above, Soengas does not teach that "LOH of any of D12S1657, D12S393, D12S1706, and D12S346 indicates that the probability for the subject to suffer from a metastatic cancer is higher than the probability for the subject to suffer from a primary cancer" recited in claim 17 or "LOH of any of D12S1657, D12S393, D12S1706, and D12S346 indicates that the probability for the subject to suffer from a progressing cancer is higher than the probability for the subject to suffer from a non-progressing cancer" recited in claim 26. Soengas also fails to teach that "wherein LOH of any of D12S1657, D12S393, D12S1706, and D12S346 indicates poor efficacy of the biochemotherapy in the subject" recited in claim 35 and "wherein LOH of any of D12S1657, D12S393, D12S1706, and D12S346 indicates a low probability of responsiveness to the biochemotherapy in the subject" recited in claim 58. Moreover, Soengas discloses nothing whatsoever about association of LOH of any of D12S1657, D12S393, D12S1706, and D12S346 with breast cancer or primary or metastatic colon cancer. Gocke does not cure the deficiencies of Soengas. Therefore, Soengas and Gocke do not add up to the instant invention, even if one skilled in the art would have been motivated to combine the two prior art references. In particular, as presented in Applicants' response to the Office Action dated October 31, 2006, it is well known in the art that in vitro experiments do not necessarily reflect the conditions in vivo. Absent any in vivo data or any established correlation between in vitro and in vivo mechanisms or results, one skilled in the art would not have reasonably expected success in applying Soengas' in vitro results to human subjects.

In conclusion, claims 1, 6, 17, 26, 35, 58, and 93 are non-obvious over the cited art for lack of reasonable expectation of success and failing to teach every limitation of the claims. Their dependent claims are also patentable for at least the same reasons. Withdrawal of the rejections is respectfully requested.

DOUBLE PATENTING

Claims 1, 6, 17, and 26 stand provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1, 7, 9, 11, 17, and 23 of co-pending U.S. Patent Application No. 10/809,956 (Applicants believe that the Examiner meant U.S. Patent Application No. 10/809,965). If the pending claims in either application are found to be otherwise allowable except for this ground of rejection, Applicants will submit an appropriate terminal disclaimer. In this event, Applicants request that the Examiner telephone the undersigned who will then provide the terminal disclaimer.

CLAIM OBJECTIONS

The Examiner objected to claims 1-6 because claim 1 recites "anddetecting." Applicants believe that the Examiner meant claims 1-3 and 5, because claim 4 was previously withdrawn from consideration and claim 6, as previously presented, does not recite "anddetecting." Applicants have corrected the typographical error by separating "and" and "detecting" in claim 1. Withdrawal of the objections is respectfully requested.

CLAIM REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH – WRITTEN DESCRIPTION – NEW MATTER

(1) Claims 1-10, 12-13, 85, 87, 89, 91, and 95 are rejected for containing new matter because they are drawn to "wherein the DNA exists as acellular DNA in the subject." Applicants respectfully point out that claims 4 and 9 were previously withdrawn from consideration and will not be discussed below.

The Examiner asserted that the specification does not provide support for "wherein the DNA exists as acellular DNA in the subject." Applicants respectfully disagree. For example, the specification describes colleting blood, separating serum from cells, and extracting DNA from the serum (page 32, lines 22-27). "Moreover, it

has been established that markedly increased concentrations of soluble DNA are present in plasma of individuals with cancer and some other diseases, indicating that cell free serum or plasma can be used for detecting cancer DNA with microsatellite abnormalities (Kamp et al., 1994, Science 264:436-440; and Steck et al., 1997, Nature Genetics 15:356-362)." See, page 8, lines 9-13 of the specification. As such, the specification, as originally filed, provides sufficient support for "wherein the DNA exists as acellular DNA in the subject."

(2) Claims 1-5 are rejected for containing new matter because they are drawn to "one or more DNA markers in the *12q22-23* region extending from D12S1657 to D12S346 on the DNA." Applicants respectfully point out that claim 4 was previously withdrawn from consideration and will not be discussed below.

Without acquiescence in the Examiner's rejections, Applicants have amended claim 1 to recite "one or more DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346 on the DNA." This amendment is supported by the specification, e.g., at page 3, lines 12-14.

In view of the foregoing, Applicants respectfully submit that claims 1 (as amended), 6, 85, 87, 89, 91, and 95 do not contain new matter. Neither do claims 2-3, 5, 7-8, 10, and 12-13, dependent from claims 1 and 6. Applicants respectfully request that the rejections be withdrawn.

CONCLUSION

Applicants believe the foregoing amendments comply with requirements of form and thus may be admitted under 37 C.F.R. § 1.116(b). Alternatively, if these amendments are deemed to touch the merits, admission is requested under 37 C.F.R. § 1.116(c). In this connection, these amendments were not earlier presented because they are in response to the matters pointed out for the first time in the Final Office Action. Lastly, admission is requested under 37 C.F.R. § 1.116(b) as presenting rejected claims in better form for consideration on appeal.

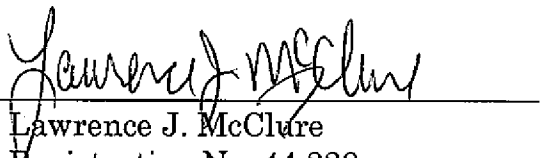
In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned at the Los Angeles, California telephone number (310)785-4600 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
HOGAN & HARTSON L.L.P.

Date: August 20, 2007

By: 

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